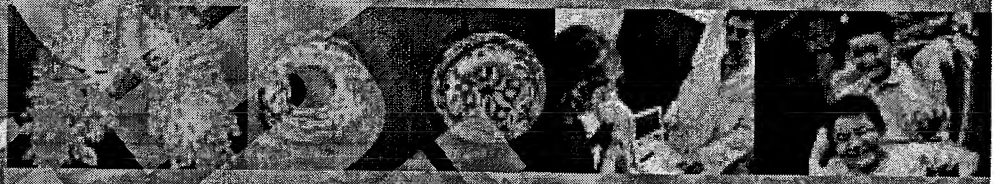
National Asthma Education and Prevention Program

EPR-3 for Practical Use

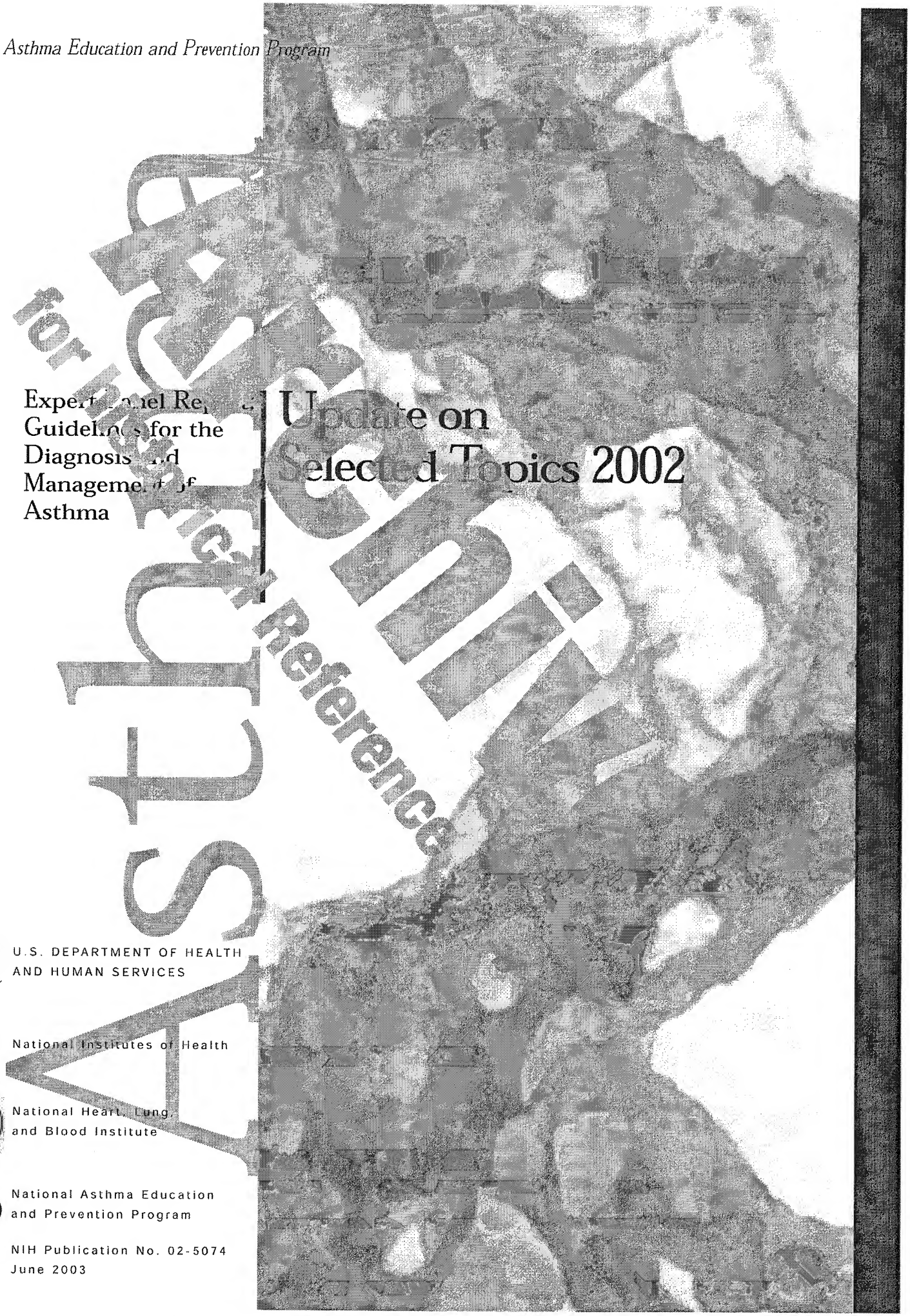
Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma

Update on Selected Topics 2002



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute

National Asthma Education and Prevention Program



Expert Panel Report
Guidelines for the Diagnosis and Management of Asthma

Update on Selected Topics 2002

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Heart, Lung, and Blood Institute

National Asthma Education and Prevention Program

NIH Publication No. 02-5074
June 2003

Contents

Expert Panel Report Guidelines for the Diagnosis and Management of Asthma

Acknowledgments

Acknowledgments

National Asthma Education and Prevention Program Science Base Committee and Expert Panel on the Management of Asthma

William W. Busse, M.D., *Chair*
University of Wisconsin Medical School
Madison, WI

Homer A. Boushey, M.D.
University of California at San Francisco
San Francisco, CA

Sonia Buist, M.D.
Oregon Health Sciences University
Portland, OR

Noreen M. Clark, Ph.D.
University of Michigan
School of Public Health
Ann Arbor, MI

H. William Kelly, Pharm.D.
University of New Mexico
Health Sciences Center
Albuquerque, NM

Robert F. Lemanske, M.D.
University of Wisconsin
Hospital and Clinics
Madison, WI

Fernando D. Martinez, M.D.
University of Arizona Medical Center
Tucson, AZ

Harold S. Nelson, M.D.
National Jewish Medical and
Research Center
Denver, CO

Gail Shapiro, M.D.
University of Washington
Seattle, WA

Stuart Stoloff, M.D.
University of Nevada School of Medicine
Reno, NV

Stanley Szefler, M.D.
National Jewish Medical and
Research Center
Denver, CO

National Heart, Lung, and Blood Institute Staff

Robinson Fulwood, Ph.D., M.S.P.H.
Senior Manager
Office of Prevention, Education, and Control

James P. Kiley, Ph.D.
Director
Division of Lung Diseases

Gregory J. Morosco, Ph.D., M.P.H.
Associate Director
Office of Prevention, Education, and Control

Diana K. Schmidt, M.P.H.
Coordinator
National Asthma Education and
Prevention Program

Virginia S. Taggart, M.P.H.
Health Scientist Administrator
Division of Lung Diseases

Prospect Associates Ltd. Staff (now part of American Institutes for Research Health Program, Silver Spring, MD)

Susan Bratten
Senior Editor

Teresa Wilson, M.P.H., R.N.
Senior Partnership Leader

National Asthma Education and Prevention Program Coordinating Committee

Claude Lenfant, M.D., *Chair*
National Heart, Lung, and Blood Institute

Denise Dougherty, Ph.D.
Agency for Health Care Policy and Research

Nancy J. Sander
Allergy and Asthma Network/Mothers of Asthmatics, Inc.

Gail Shapiro, M.D.
American Academy of Allergy, Asthma, and Immunology

Barbara P. Yawn, M.D., M.Sc.
American Academy of Family Physicians

Gary S. Rachelefsky, M.D.
American Academy of Pediatrics

Gabriel R. Ortiz, M.P.A.S., PA-C
American Academy of Physician Assistants

Thomas J. Kallstrom, R.R.T.
American Association for Respiratory Care

Pam Carter, R.N., C.O.H.N.-S.
American Association of Occupational Health Nurses

William Storms, M.D.
American College of Allergy, Asthma, and Immunology

John P. Mitchell, M.D., F.A.C.P.
American College of Chest Physicians

Richard M. Nowak, M.D., M.B.A., F.A.C.E.P.
American College of Emergency Physicians

Noreen M. Clark, Ph.D.
American Lung Association

Paul V. Williams, M.D.
American Medical Association

Karen Huss, R.N., D.N.Sc.
American Nurses Association

Dennis M. Williams, Pharm.D.
American Pharmaceutical Association

Pamela J. Luna, Dr.P.H., M.Ed.
American Public Health Association

Lani S.M. Wheeler, M.D., F.A.A.P., F.A.S.H.A.
American School Health Association

Leslie Hendeles, Pharm.D.
American Society of Health-System Pharmacists

Stephen C. Lazarus, M.D.
American Thoracic Society

Barbara L. Hager, M.P.H., C.H.E.S.
Association of State and Territorial Directors of Health Promotion and Public Health Education

Mary E. Worstell, M.P.H.
Asthma and Allergy Foundation of America

Sarah Lyon-Callo, M.A., M.S.
Council on State and Territorial Epidemiologists

Carol Costante, R.N., M.A., C.S.N., F.N.A.S.N.
National Association of School Nurses

Susan B. Clark, R.N., M.N.
National Black Nurses Association, Inc.

Mary Vernon-Smiley, M.D., M.P.H.
National Center for Chronic Disease Prevention
Centers for Disease Control and Prevention

Leslie P. Boss, Ph.D., M.P.H.
National Center for Environmental Health
Centers for Disease Control and Prevention

Lara Akinbami, M.D.
National Center for Health Statistics
Centers for Disease Control and Prevention

Gregory R. Wagner, M.D.
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

Kenneth Adams, Ph.D.
National Institute of Allergy and Infectious Diseases

J. Patrick Mastin, Ph.D.
National Institute of Environmental Health Sciences

Michael Lenoir, M.D.
National Medical Association

Ruth I. Quartey, M.A., R.R.T.
NHLBI Ad Hoc Committee on Minority Populations

Carlos A. Camargo, M.D., Dr.P.H.
Society for Academic Emergency Medicine

Estelle Bogdonoff, M.P.H., C.H.E.S.
Society for Public Health Education

Doris Sligh
U.S. Department of Education

David E. Jacobs, Ph.D.
U.S. Department of Housing and Urban Development

Mary T. Smith, J.D.
U.S. Environmental Protection Agency

Robert J. Meyer, M.D.
U.S. Food and Drug Administration

Olivia Carter-Pokras, Ph.D.
U.S. Public Health Service

Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma

Preface

Asthma for Medical Reference

Preface

Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002 (EPR—Update 2002) provides timely information on several selected priority asthma topics. It updates recommendations of the *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* (EPR-2).

The current update was developed using a new approach that will make the asthma guidelines a dynamic and timely guide for practicing clinicians. The National Asthma Education and Prevention Program (NAEPP) Science Base Committee regularly reviews the scientific literature as an ongoing process to identify topics that warrant a more in-depth and systematic review. For this update, the Committee has focused on a few of the more pressing asthma issues rather than updating all topics at once. This approach should provide more expeditious updates in the future, thus adding to the value of the guidelines as a living document.

The Committee recommends to the NAEPP Coordinating Committee when a review is warranted and, upon concurrence by the CC, an expert panel is convened. Expert panel members are independent thinkers who represent a multidisciplinary group of clinicians and scientists possessing expertise in clinical management. They make recommendations based on their interpretation of the best and most current evidence available.

The 2002 update to the asthma guidelines has been developed under the able leadership of Dr. William Busse, Panel Chair. The National Heart, Lung, and Blood Institute sincerely appreciates the work of Dr. Busse and all members of the Expert Panel in developing this report. Sincere appreciation also goes to the 40 organizations (professional societies, voluntary organizations, Federal agencies) that comprise the NAEPP-CC for their thoughtful review and comments in approving content of this report.

Ultimately, broad change in clinical practice depends on the influence of local physicians and other health professionals who not only provide state-of-the-art care to their patients, but also communicate to their peers the importance of doing the same. We are optimistic that over the next several years, the joint efforts of the NAEPP, its CC member organizations, and committed professionals at the local level will result in extensive implementation of the recommendations in the EPR—Update 2002 and EPR-2. We ask for the assistance of every reader in reaching our ultimate goal: improving asthma care and the quality of life for every patient with asthma and their families.

Publications from the NAEPP can be ordered through the National Heart, Lung, and Blood Institute Information Center, P.O. Box 30105, Bethesda, MD 20924-0105. Publications are also available through the Internet at www.nhlbi.nih.gov/nhlbi.htm.

Claude Lenfant, M.D.
Director
National Heart, Lung, and Blood Institute
Chair, National Asthma Education and Prevention Program Coordinating Committee

Introduction

Expert Panel Report
Guidelines for the
Diagnosis and
Management of
Asthma

Introduction

Asthma is a chronic inflammatory disease of the airways that has created a significant public health burden. In the United States, more than 11 million people reported having an asthma attack in the year 2000, and more than 5 percent of all children younger than age 18 reported having asthma attacks. In 1999, asthma was responsible for 2 million emergency department visits, 478,000 hospitalization with asthma as a primary diagnosis, and 4,426 deaths. The rates of hospitalization have remained the same or lower since 1980 for all age groups, except children younger than age 15. Mortality rates have declined overall since 1995, but a disparity among ethnic groups remains. Asthma mortality is nearly 3 times higher in black males than in white males and 2.5 times higher in black females than in white females (Centers for Disease Control and Prevention).

Scientific advances over the last 15 years have led to a greater understanding of the mechanisms of asthma and the development of therapeutic approaches that can reduce morbidity and improve the quality of life among persons with asthma. To help health care professionals bridge the gap between current knowledge and practice, the National Heart, Lung, and Blood Institute's (NHLBI's) NAEPP has convened expert panels to prepare clinical practice guidelines for the diagnosis and management of asthma. The NAEPP Coordinating Committee, under the leadership of Claude Lenfant, M.D., director of the NHLBI, convened the first Expert Panel in 1989. The Panel was charged with developing a report that would provide a general approach to diagnosing and managing asthma based on current science. The NAEPP *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma* (NAEPP 1991) was published in 1991. Recommendations for the treatment of asthma were organized around the following four components of effective asthma management:

- Use of objective measures of lung function to assess the severity of asthma and to monitor the course of therapy
- Environmental control measures to avoid or eliminate factors that contribute to asthma severity
- Comprehensive pharmacologic therapy for long-term management designed to reverse and prevent the airway inflammation characteristic of asthma, as well as pharmacologic therapy to manage asthma exacerbations
- Patient education that fosters a partnership among the patient, his or her family, and clinicians.

The NAEPP convened a second Expert Panel in 1995 to review the entire 1991 report and update it, if necessary, based on review of the literature published since 1991 and on clinical experience with implementation of the report's recommendations for clinical practice. The NAEPP *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma* (EPR-2) was published in 1997.

The NAEPP recognizes that the value of clinical practice guidelines lies in their presentation of recommendations based on the best and most current evidence available. However, high-quality research on all areas of asthma management is not available, and scientific examination and discovery often is focused on only a few areas at any given time. The NAEPP concluded that an efficient approach to updating the clinical practice guidelines would be to identify selected questions that warrant intensive review and possible update, based on either the level of research activity reflected in the published literature or the level of concern or controversy in clinical practice. Position statements on these topics would be published as NAEPP *Expert Panel Report Updates*, and would be incorporated into the

Web-based version of EPR-2. Thus, the NAEPP *Expert Panel Report* is a dynamic document that will be updated continuously with position statements on topics of interest to the community of patients, clinicians, and organizations dedicated to improving asthma care.

The NAEPP charged its Science Base Committee with the responsibility for monitoring the scientific literature, identifying topics for review, determining the need for changes in the EPR-2, and preparing appropriate updates. The Science Base Committee is a multidisciplinary group of clinicians and scientists with expertise in asthma management. The group includes health professionals in the areas of general medicine, family practice, pediatrics, emergency and critical care, allergy, pulmonary medicine, pharmacy, and health education. The Science Base Committee reports to the NAEPP Coordinating Committee, which comprises representatives from 40 professional societies, voluntary organizations, and Federal agencies.

This report, the NAEPP *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002* (EPR—Update 2002), presents recommendations for the management of asthma that will help clinicians and patients make appropriate decisions about asthma care on the following topics:

- Medications
  - Long-term management of asthma in children:
    - Effectiveness of inhaled corticosteroids for children with mild or moderate persistent asthma compared with other medications
    - Safety of long-term use of inhaled corticosteroids
  - Combination Therapy: The addition of other long-term-control medications to inhaled corticosteroids
  - The effect of antibiotics on acute asthma exacerbations
- Monitoring
  - Written asthma management plans compared to medical management alone
  - Peak flow-based compared to symptom-based written action plans
- Prevention
  - Effects of early treatment on the progression of asthma.

The appendices to this report contain updated stepwise and dosage charts and a list of abbreviations and acronyms.

This report revises the EPR-2 Stepwise Approach for Managing Asthma to incorporate findings from the review of the scientific evidence. These guidelines are intended to inform, not replace, clinical judgment. Of course, the clinician and patient need to develop individual treatment plans that are tailored to the specific needs and circumstances of the patient. This report is not an official regulatory document of any Government agency.

...ds ... To Develop This Report

The NAEPP Science Base Committee met in April 1999 to identify priority areas for review and possible update of recommendations in EPR-2. The Committee used a modified Delphi technique to rank all major EPR-2 clinical recommendations according to whether major new studies had been published in that area or the area was of considerable clinical interest but lacking in consistent evidence at the time EPR-2 was developed. At the same time, the Agency for Healthcare Research and Quality (AHRQ), through its own routine process of soliciting questions from the medical community for the development of evidence reports, received questions on asthma from the American Academy of Pediatrics and the American Academy of Family Physicians. Several of the topics were comparable to those identified by NAEPP Science Base Committee, so the NHLBI worked with the AHRQ to develop a contract with an AHRQ Evidence-Based Practice Center. An AHRQ contract was awarded to the Blue Cross Blue Shield Association Technology Evaluation Center to conduct a systematic review of the evidence (SRE) on the topics listed earlier.

In August 1999, the AHRQ Evidence-Based Practice Center began to perform comprehensive review of the literature on each of the selected topics; to prepare evidence tables depicting study design, research

variables, and reported outcomes; and to summarize the literature findings in a narrative report. This report, however, was not intended to make judgments about the implications of the findings for clinical practice. The Evidence-Based Practice Center's methods for conducting the SRE are described in detail elsewhere (Blue Cross and Blue Shield Association Technology Evaluation Center) and are summarized here.

The Evidence-Based Practice Center formed a Technical Advisory Group composed of asthma specialists and primary care physicians, including several members of the NAEPP Science Base Committee. The literature search included full-length reports published in peer-reviewed medical journals and articles in English or published in foreign languages with English abstracts. Studies that did not include control groups in the research design were excluded from review (except for those that dealt with the topic of adverse effects of inhaled corticosteroids), and most of the included trials were randomized. Specific criteria that defined patient populations of interest, outcomes of interest, types of interventions, and study design were established for each topic. A comprehensive literature search was performed using key text words and MeSH terms (Medical Subject Heading) to identify all relevant controlled clinical trials. (Key words included, for example, all long-term-control asthma medications, antibiotics in asthma, peak expiratory flow rate meter, action plan, and self-care monitoring.) Both the MEDLINE and EMBASE databases were searched for all articles published from 1980 through August 2000. In addition, the search included potentially relevant studies published before 1980 but referenced in the post-1980 literature.

- The search retrieved 4,235 English and 343 non-English language references. One member of the Evidence-Based Practice Center's study team reviewed abstracts; a second team member reviewed any excluded abstracts. On the basis of this abstract review, 668 full-length journal articles were retrieved and rated independently by two study team members against study selection criteria. Eighty-seven articles met the study selection criteria to be included in the SRE. Data from these 87 articles were abstracted for evidence tables by two reviewers and were recorded in an electronic database. Data elements included categories such as study design and methods, patient characteristics, lung function outcomes, symptom outcomes, medication outcomes, utilization outcomes, and adverse events.

- A quality assessment of the studies was performed to enable sensitivity analysis comparing the results and conclusions reached from all included studies with the results and conclusions of a subgroup of higher quality studies. Quality was assessed on three domains: concealment of treatment allocation during randomization, double-blinding, and handling of withdrawals and exclusions. Quality also was assessed on domains deemed pertinent to asthma research, such as establishing reversibility of airway obstruction, controlling for other medication use, reporting compliance, addressing seasonality, and a priori reporting of power calculations.

- A meta-analysis was performed to assess the benefits of adding long-acting inhaled $beta_2$ agonist medication to inhaled corticosteroids as treatment of moderate persistent asthma.

In February 2001, the Evidence-Based Practice Center submitted a draft report of the SRE to the AHRQ. The NAEPP Science Base Committee, serving as an Expert Panel, met in March to review the Evidence-Based Practice Center's report and to interpret the implications for clinical practice and the recommendations included in EPR-2. The Expert Panel reached consensus on whether the evidence supported the recommendations made in EPR-2 or indicated a need for revision. The Expert Panel then assigned writing committees to develop position statements on each of the topics. Each Panel member was assigned to one of the writing committees. The Expert Panel noted that, for some topics, significant studies had been published in the 7-month period between the Evidence-Based Practice Center's search of the literature and the submission of its report. The Expert Panel agreed that the writing committees would include their own review of additional literature published since August 2000 and use MEDLINE searches as appropriate. The distinction between the two literature reviews is noted in the position statements by separating discussion of the Evidence-Based Practice Center's SRE and the Expert Panel's *Additional Literature or Information.* Further, the

source and level of the evidence used to justify Panel recommendations for sustaining or revising EPR-2 are noted in parentheses following the recommendation. (That is, the level of evidence is categorized A, B, C, or D according to the description below. If the source of the evidence is from the SRE, the category is preceded by the notation "SRE"; if the source is the Expert Panel's additional literature, there is no prefix.) The system used to describe the level of evidence is as follows (Jadad et al. 2000):

- **Evidence Category A: Randomized controlled trials (RCTs), rich body of data.** Evidence is from end points of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.

- **Evidence Category B: RCTs, limited body of data.** Evidence is from end points of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.

- **Evidence Category C: Nonrandomized trials and observational studies.** Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.

- **Evidence Category D: Panel consensus judgment.** This category is used only in cases where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel consensus is based on clinical experience or knowledge that does not meet the criteria for categories A through C.

As the Expert Panel members reviewed the scientific evidence and considered revisions to EPR-2, they identified areas that require further investigation to either fill important gaps found in the data or to pursue promising areas of research revealed by study findings. Each position statement includes recommendations for further research.

The Expert Panel prepared draft position statements in its respective writing committees during summer and fall 2001, and the drafts were edited during the winter. A series of drafts were discussed in three telephone conference calls (June 2001, October 2001, and February 2002) among the full Panel membership. Final agreement on each position statement was reached during these calls, including the specific recommendations within the position statements to either retain or revise EPR-2. A vote confirmed the unanimous agreement of the Panel. In March 2002, a draft was mailed to the NAEPP Coordinating Committee members for their review, comment, and approval. In April 2002, the Expert Panel reviewed the Coordinating Committee's suggested edits by e-mail and by telephone conference call and incorporated suggestions that were within the scope of the Coordinating Committee's approval. Expert Panel members' agreement on the final text was unanimous. The NAEPP EPR—Update 2002 was released in June 2002.

This report was funded by the NHLBI, National Institutes of Health. Expert Panel members disclosed relevant financial interests to each other prior to their deliberations. Expert Panel members and reviewers participated as volunteers and were compensated only for travel expenses related to the Expert Panel meeting.

In summary, the NAEPP *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002* represents the NAEPP's ongoing effort to keep recommendations for clinical practice up to date and based on systematic review and consideration of the best available scientific evidence, as well as on the collective expertise of the Expert Panel and Coordinating Committee members in asthma management. The NAEPP hopes that this report will assist clinicians and patients as they work together to achieve asthma control.

References

Blue Cross and Blue Shield Association Technology Evaluation Center. *Evidence Report/Technology Assessment Number 44.* Agency for Healthcare Research and Quality Publication No. 01-EO-44. Rockville, MD, 2001.

Centers for Disease Control and Prevention.

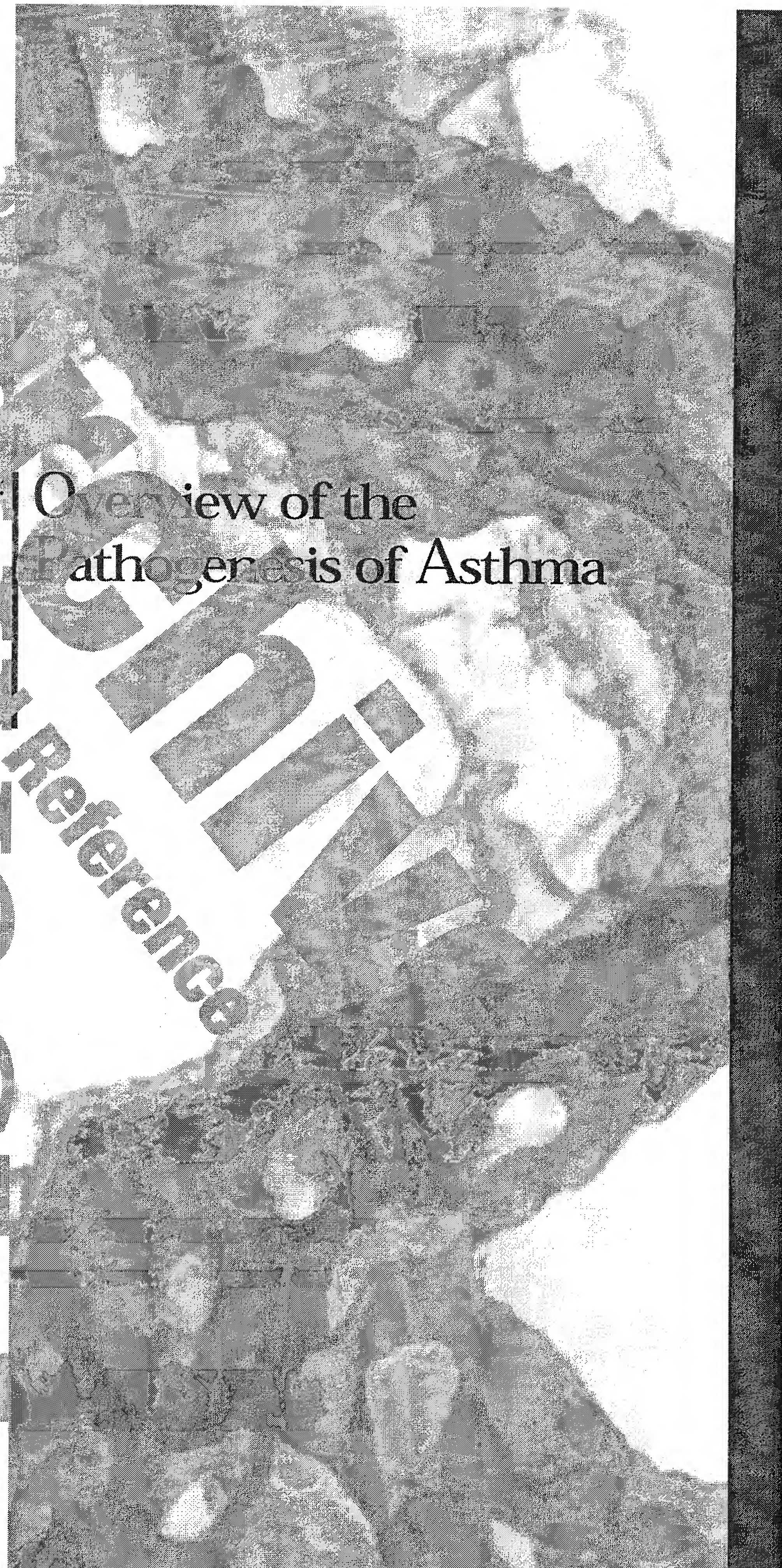
Jadad AR, Moher M, Browman GP, Booker L, Sigouin C, Fuentes M, Stevens R. Systematic reviews and meta-analyses on treatment of asthma: critical evaluation. *BMJ* 2000;320(7234):537–40.

Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for Asthma—United States, 1980–1999. *MMWR Surveillance Summaries* 2002;51(SS01):1–13.

National Asthma Education and Prevention Program. *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma.* National Institutes of Health Publication No. 91-3642. Bethesda, MD, 1991.

National Asthma Education and Prevention Program. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma.* National Institutes of Health Publication No. 97-4051. Bethesda, MD, 1997.

Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma



Overview of the Pathogenesis of Asthma

Overview of the Pathogenesis of Asthma

An overview of current insights into the pathophysiology of asthma is presented here in order to provide a context in which recommendations regarding asthma treatment were made for the *EPR—Update 2002.*

The working definition of asthma, as proposed in the EPR-2 in 1997 (page 3)—

> *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli (NHLBI 1997).*

—continues to capture the features of asthma and underscores the importance of airway inflammation to the pathogenesis, pathophysiology, and treatment of this disease. Important additions to this definition include recent observations that reversibility may be incomplete in some patients with asthma, and other individuals with features of chronic bronchitis may manifest some degree of reversibility in airflow obstruction (Bousquet J. et al. 2000). Nonetheless, the study of asthma pathogenesis and its treatment continues to focus on inflammation as a target to control and regulate airflow obstruction and the resulting symptoms.

Recent studies have begun to categorize airway inflammation into phases, which although somewhat arbitrary in demarcation, provide insights into the possible progression of the disease as well as its management. Acute symptoms of asthma usually arise from bronchospasm and require and respond to bronchodilator therapy. Acute and chronic inflammation can affect not only the airway caliber and airflow but also underlying bronchial hyperresponsiveness, which results in susceptibility to bronchospasm. Treatment with anti-inflammatory drugs can, to a large extent, reverse some of these processes; however, the successful response to therapy often requires weeks to achieve and, in some situations, may be incomplete. Finally, some patients may have persistent airflow limitations for which no current therapy has been found to be effective. Therefore, the paradigm of asthma has been expanded from bronchospasm and airway inflammation to include airway remodeling in some patients. The concept that asthma may be a continuum of these processes that can lead to moderate and severe persistent disease is of critical importance to understanding this disease's pathogenesis and pathophysiology. As these questions undergo a constant evaluation, current treatment recommendations also must be reassessed.

[illegible] of Asthma

Airway inflammation in asthma is found in patients with mild, moderate, and severe disease. Although there are some universal features of this inflammatory response in the airway, the specifics of the bronchial reaction show variations, which are dependent upon the disease's severity, treatment, and duration. Infiltration of the airway by inflammatory cells such as activated lymphocytes and eosinophils, denudation of the epithelium, deposition of collagen in the subbasement membrane area, and mast cell degranulation are often, but not always, features of mild or moderate persistent asthma. In fatal disease and severe persistent asthma, other conditions occur, such as occlusion of the bronchial lumen by mucus, hyperplasia and hypertrophy of the bronchial smooth muscle, and goblet cell hyperplasia.

The cellular profile of inflammation in asthma provides evidence for the nature of the immune reaction of injury and remodeling or repair, the potential mechanisms by which such responses occur, the resulting alteration in physiology, and the possible therapeutic targets necessary to regulate, reverse, or prevent such events. IgE antibodies have been found to have a relationship to the severity of asthma and the airway's early response to allergens. The ability to synthesize IgE antibodies to environmental allergens (i.e., atopy) remains a major risk factor in asthma pathogenesis. Synthesized IgE binds to mast cells and basophils via high-affinity IgE receptors, and the bridging of these attached molecules signals the cells to release preformed and newly generated mediators, including histamine and cysteinyl leukotrienes, to rapidly contract airway smooth muscle. In addition, the mast cell can produce a variety of cytokines, including interleukin (IL)-1, -2, -3, -4, and -5 along with granulocyte-macrophage colony-stimulating factor, interferon (IFN)-γ, and tumor necrosis factor-α. The generation of these pro-inflammatory proteins suggests that mast cells can contribute to both acute and chronic inflammation.

Eosinophilic infiltration of the airway remains a consistent feature of acute inflammation and also is found in mucosal airway tissue from many patients with chronic, persistent asthma. The granule proteins of the mature eosinophil are sources of inflammatory mediators, including major basic protein, which can injure airway epithelium, enhance bronchial responsiveness, and affect the regulation of acetylcholine release. In addition, the eosinophil can release cysteinyl leukotrienes, such as C_4, to contract airway smooth muscle. The production of eosinophils and their release from the bone marrow are regulated by IL-5. Migration of these cells to the airway involves an interaction of eosinophil surface-bound integrins, β_1 and β_2, with endothelial cell and matrix tissue counterligands. Finally, recently identified families of chemokines (RANTES) eotaxin, and macrophage inflammatory protein-1α, participate in the migration of these cells to the airway. Although the eosinophil is a feature of asthma pathology that is known to be affected by anti-inflammatory therapy in a manner that improves airway physiology, its precise role in the pathophysiology of asthma is still under investigation.

An Imbalance Between Th1 and Th2 in the Origins of Asthma

The role of lymphocytes in the inception and progression of asthma continues to be of considerable importance. Since the 1997 EPR-2, there has been interest in the idea that an imbalance in T-helper (Th) 1 and Th2 cytokines may help explain and even predict the subsequent development of asthma. Airway inflammation in asthma may represent a loss of normal balance between two "opposing" populations of Th lymphocytes. Two types of Th lymphocytes have been characterized: Th1 and Th2. Th1 cells produce IL-2 and IFN-γ, which are critical in cellular defense mechanisms in response to infection. Th2, in contrast, generates a family of cytokines (IL-4, -5, -6, -9, and -13) that can mediate allergic inflammation. The current "hygiene hypothesis" of asthma illustrates how this cytokine imbalance may explain some of the dramatic increases in asthma prevalence in Westernized countries. This hypothesis is based on the assumption that the immune system of the newly born is skewed towards Th2 cytokine generation. Following birth, environmental stimuli such as infections will activate Th1 responses and bring the Th1/Th2 relationship to an appropriate balance. There is evidence that the incidence of asthma is reduced in association with certain infections (*M. tuberculosis*, measles, or hepatitis A); exposure to other children (e.g., presence of older siblings and early enrollment in childcare); and less frequent use of antibiotics. Furthermore, the absence of these lifestyle events is associated with the persistence of a Th2 cytokine pattern. Under these conditions, the genetic background of the child, with a cytokine imbalance toward Th2, will set the stage to promote the production of IgE antibody to key environmental antigens, such as house dust mite, cockroach, *Alternaria*, and possibly cat. Therefore, a gene-by-environment interaction occurs in which the susceptible host is exposed to environmental factors that are capable of generating IgE, and sensitization occurs. Precisely why the airways of some individuals are susceptible to these allergic events is not established.

There also appears to be a reciprocal interaction between the two subpopulations in which Th1 cytokines can inhibit Th2 generation and vice versa.

Allergic inflammation may be the result of an excessive expression of Th2 cytokines. Alternately, the possibility that the loss of normal immune balance arises from a cytokine dysregulation in which Th1 activity in asthma is diminished has been suggested in recent studies. The focus and actions of cytokines and chemokines to regulate and activate the inflammatory profile in asthma has provided ongoing and new insight into the pattern of airway injury that may lead to new therapeutic targets.

Because of the importance of IgE to the pathogenesis of allergic diseases and inflammation, the development of humanized monoclonal antibodies has become a possible treatment. Early studies in asthma have indicated that this approach can reduce serum IgE, inhibit the immediate and late airway response to inhaled antigen, and allow for a withdrawal of inhaled corticosteroids without deterioration in lung function or precipitation of an asthma exacerbation. The findings of anti-IgE monoclonal antibody therapy support the importance of IgE-mediated responses in asthma and suggest that IgE-regulated processes may encompass processes that influence inflammation other than mast-cell-dependent responses.

In addition, monoclonal antibodies against IL-5 recently have been tested in asthma. Anti-IL-5 has reduced circulating concentrations of eosinophils and their presence in sputum. However, despite the reduction (but not elimination) of eosinophils, there was no change in the development of the late-phase response to an inhaled antigen. These preliminary studies have raised questions about the specific role of IL-5 in mechanisms of airflow obstruction and of eosinophils in the pathophysiology of asthma. It appears to be an omnipresent cell in asthma, but how it participates in the disease process is not yet clear.

A soluble IL-4 receptor (IL-4R) has been developed for inhaled administration. This molecule acts as a decoy and is capable of binding to IL-4 and thus acting as an antagonist for that molecule. Although early studies that administered nebulized IL-4R showed that inhaled corticosteroid doses can be reduced without a loss of asthma control or lung function, subsequent trials with this molecule have failed to demonstrate effectiveness in asthma control.

A number of lessons can be learned from these early studies directed toward a single cytokine. Although modification of features of allergic inflammation can be seen in animals with genes that have "knocked out" selected cytokines, similar benefits have not necessarily been seen in human asthma. These findings underscore the relevancy of multiple factors regulating inflammation in asthma and the redundancy of these processes. Moreover, these clinical studies in human asthma also serve to indicate that phenotypes of asthma exist and that these phenotypes may have very specific patterns of inflammation. Nonetheless, as more clinical trials with modifiers of inflammation in asthma are performed, it is likely that a more comprehensive insight into the mechanisms of this disease will occur.

In summary, recent evidence continues to underscore the importance of immune factors in the development of asthma and resulting inflammation processes. Insight into the mechanisms of these processes will be important for future therapy. In the meantime, asthma therapy continues to focus on controlling underlying airway inflammation.

References

Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med* 2000;161(5):1720–45.

Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma

1. Medications

Asthma

1. Medications

Several clinical questions were considered by the NAEPP Expert Panel regarding medications used in asthma therapy, including questions about the effectiveness of inhaled corticosteroids compared to other long-term-control medications in the management of asthma in children, the safety of long-term use of inhaled corticosteroids in children, the use of combination therapy in treating moderate persistent asthma, and the use of antibiotics in treating acute exacerbations of asthma. This section on medications will present each clinical question separately, and each discussion will include a statement of the specific question; a summary answer to the question; the rationale for the question; a summary of the SRE, as well as additional literature considered by the Expert Panel after the systematic review was completed; recommendations for updating the EPR-2 and recommendations for future research.

Long-Term Management of Asthma in Children: Effectiveness of Inhaled Corticosteroids Compared to Other Medications

Question

Does chronic use of inhaled corticosteroids improve long-term outcomes for children with mild or moderate persistent asthma, in comparison to the following treatments?

- ***"As-needed" beta$_2$-agonists?***
- ***Long-acting beta$_2$-agonists?***
- ***Theophylline?***
- ***Cromolyn/nedocromil?***
- ***Combinations of above drugs?***

Leukotriene modifiers (leukotriene receptor antagonists [LTRAs] and 5-lipoxygenase inhibitors) were not included in the SRE because no published data meeting minimal inclusion criteria for children were available to compare this class of compounds directly to any other long-term-control medications, including inhaled corticosteroids. Studies on LTRAs in children that were published subsequent to the SRE were considered by the Expert Panel as additional information and included in the comprehensive review of the question.

Summary Answer to the Question

Strong evidence establishes that inhaled corticosteroids improve long-term outcomes for children of all ages with mild or moderate persistent asthma, compared to as-needed beta$_2$-agonists, as measured by prebronchodilator forced expiratory volume in 1 second (FEV_1), reduced hyperresponsiveness, improvements in symptom scores, fewer courses of oral corticosteroids, and fewer urgent care visits or hospitalizations (SRE-Evidence A). Studies comparing inhaled corticosteroids to cromolyn, nedocromil, theophylline, or LTRAs are limited, but available evidence shows that none of these long-term-control medications is as effective as inhaled corticosteroids in improving asthma outcomes (SRE-Evidence B; Evidence B, C). (See Appendix A, Stepwise Approach for Managing Asthma, for the definition of asthma severity classifications.) A revision to the EPR-2 stepwise approach to therapy is recommended. The Expert Panel recommends the following therapy for children with mild persistent asthma:

- For children older than 5 years of age, the preferred therapy is inhaled corticosteroids (low dose) (SRE-Evidence A). Alternative therapies (listed alphabetically because there are insufficient data to enable ranking) include cromolyn, LTRAs, nedocromil, or sustained-release theophylline (SRE-Evidence A, B; Evidence A, B).

- For children 5 years of age and younger, no studies compare inhaled corticosteroids to other long-term-control medications. Therefore, recommendations are based on extrapolations of studies in older children. The preferred therapy is low-dose inhaled corticosteroids, with nebulizer, dry powder inhaler (DPI), or metered-dose inhaler (MDI) with holding chamber, with or without a face mask. Alternative therapies (listed alphabetically) include cromolyn or LTRA (SRE-Evidence B).

Rationale for the Questi

The NAEPP recognizes the need for continual appraisal of the benefits and potential risks of asthma medications in children. The EPR-2 recommends inhaled corticosteroids, cromolyn, and nedocromil as preferred treatment, with acknowledgement of a potential but small risk of adverse events with the use of inhaled corticosteroids. The NAEPP considers it important to update information regarding the effectiveness and safety of inhaled corticosteroids in children. A review of evidence on the safety of inhaled corticosteroids is presented in another section. To enrich the evaluation of effectiveness, the SRE searched the literature for studies comparing the effectiveness of inhaled corticosteroids used as monotherapy to short-acting beta$_2$-agonists taken as needed, and to other long-term-control medications used as monotherapy in children with mild or moderate persistent asthma. Such a review enables the NAEPP to consider the most appropriate position of various medications in the stepwise approach to asthma management, based on the current evidence. At the time that the EPR-2 was published, the following long-term-control medications were available for treatment in children: inhaled corticosteroids, long-acting inhaled beta$_2$-agonists (salmeterol), theophylline, cromolyn, nedocromil, and leukotriene modifiers (zafirlukast and zileuton); not all were approved for use in children younger than 5 years of age. Since the publication of the EPR-2, a third leukotriene modifier, montelukast, has become available for children 2 years of age and older, and a nebulized form of inhaled corticosteroids has become available for children as young as 1 year of age. The DPI forms of salmeterol and fluticasone, available for older children, also were approved down to 4 years of age.

Systematic Review of the Evidence

The following description of the SRE is an adaptation of the evidence report, including direct excerpts, submitted by the Blue Cross Blue Shield Association Evidence-Based Practice Center. (See Introduction, Methods.)

Methods of Literature Search

This question addresses long-term outcomes of treatment for children with mild or moderate persistent asthma. Outcomes of primary interest are those that indicate the progression of underlying disease; short-term measures of symptom control cannot adequately address this question. Of the available measures, longitudinal determination of postbronchodilator FEV_1 provides the best available measure of lung growth (CAMP Research Group 2000). Epidemiologic studies often use prebronchodilator FEV_1, which has been one of the strongest correlates with long-term outcomes. Peak expiratory flow (PEF) also can indicate long-term progression; both prebronchodilator FEV_1 and PEF are more subject to short-term changes in control and, of the two, PEF is the more variable measure. Other outcome measures, such as symptoms, medication use, and utilization measures, also are likely to correlate with long-term progression of disease over time, but are highly subject to changes in short-term control of bronchospasm.

In addition to the eligibility criteria for selecting studies related to all topics in the SRE (described in the Introduction), the following criteria were used to select studies for this question:

- Study design is a comparative or crossover clinical efficacy trial, with a concurrent control group.
- Study compares the use of inhaled corticosteroids vs. placebo; OR compares inhaled corticosteroids vs. no treatment control; OR compares inhaled corticosteroids vs. alternative medication for mild asthma (as-needed beta$_2$-agonists, theophylline, cromolyn, nedocromil, or combinations of these medications); OR compares *the addition of* inhaled corticosteroids to other medication for mild asthma (as-needed beta$_2$-agonists, theophylline, cromolyn, nedocromil, or combinations of these medications).

- Includes at least 10 evaluable, similarly treated patients per study arm or crossover phase with mild or moderate persistent asthma, with the following defined limits:
  - FEV_1 more than 60 percent of predicted; PEF variability more than 20 percent

  OR
  - Symptoms more than 2 times a week to daily

  OR
  - Nocturnal symptoms more than 2 times a month

  OR
  - Population cannot be classified into the above categories but appears to include primarily persons with mild or moderate persistent asthma

  OR
  - Population is mixed, but the majority appears to consist of persons with mild or moderate persistent asthma.

- Study duration is of at least 12 weeks.

- At least 90 percent of included patients have not been treated with other long-term-control medications (LTRAs, long-acting inhaled $beta_2$-agonists, inhaled corticosteroids) for at least 4 weeks before beginning to take inhaled corticosteroids.

- Enrolls only patients younger than 18 years of age or stratifies outcomes for patients younger than 18 years of age.

- Study addresses relevant outcomes.

Summary of Findings

Studies

Ten studies enrolling 2,210 patients met the inclusion criteria for this question. Three of the studies were based in the Netherlands (Hoekstra et al. 1996; Van Essen-Zandvliet et al. 1992; Verberne et al. 1997); two were from Scandinavia (Jonasson et al. 1998; Agertoft and Pedersen 1994); two from the United Kingdom (Storr et al. 1986; Connett et al. 1993); two from the United States (CAMP 2000; Tinkelman 1993); and one from Canada (Simons 1997). Nine of the 10 studies were randomized, double-blind, parallel-group trials. The most robust of these, the Childhood Asthma Management Program (CAMP) Research Group (CAMP 2000), is a three-arm trial enrolling 1,041 patients followed for 4 to 6 years that compared inhaled corticosteroids to nedocromil and with placebo. At present, the CAMP trial is the "largest, longest, and most comprehensive multicenter treatment trial for asthma ever attempted in the United States"(CAMP 2000). The remaining eight randomized trials are considerably smaller in size (range: 14 to 102 patients per study arm) and duration of followup (range: 1 to 2 years). The tenth trial (Agertoft and Pedersen 1994) was not randomized. (See the key evidence tables in this section for a summary description of the 10 studies that met the eligibility criteria for evaluation.) Publications comparing the use of LTRA in children to other long-term-control medications were not available at the time of the SRE.

Results of Studies

Inhaled Corticosteroids Compared to As-Needed $Beta_2$-Agonists

Children Older than 5 Years of Age

The evidence of the efficacy of inhaled corticosteroids in children older than 5 years of age was obtained from six trials, five of which were placebo controlled and randomized. These six trials enrolled a total of 790 patients treated with inhaled corticosteroids and 652 controls. The most robust evidence is from the CAMP trial, which contributed 40 percent (311) of the total inhaled corticosteroid patients and 64 percent (418) of the total controls, documented the longest duration of treatment (4 years), used the most complete outcome measures, and reported in the greatest detail the study design and statistical analysis.

Overall, these studies demonstrate that inhaled corticosteroids improve asthma control compared to as-needed $beta_2$-agonists without any other long-term-control medication. Inhaled corticosteroid-treated patients with mild or moderate persistent asthma demonstrate improvements in prebronchodilator FEV_1, reduced airway hyperresponsiveness, symptom scores and symptom frequency, less supplemental $beta_2$-agonist use, fewer courses of oral corticosteroids, and lower hospitalization utilization. The evidence does not

suggest, however, that inhaled corticosteroid use is associated with improved long-term postbronchodilator FEV_1 which is a surrogate measure of lung growth. The CAMP trial reported no difference in the change in postbronchodilator FEV_1 after 4 years of treatment (CAMP 2000). No study reported any statistically significant result that favored the as-needed $beta_2$-agonist control group.

Children 5 Years of Age or Younger

Two small trials (69 participants, combined) compared inhaled corticosteroid treatment to placebo in children younger than 5 years of age. The available evidence is scant, but the results reported appear to be consistent with those reported for children older than 5 years of age: that inhaled corticosteroids improve short-term control of asthma. No studies that examine the long-term impact of inhaled corticosteroids on lung function in this age group are available.

Inhaled Corticosteroids Compared to Alternative Long-Term-Control Medications

No comparison studies are available for children younger than 5 years of age.

Long-Acting Inhaled $Beta_2$-Agonist (Salmeterol)

The available evidence is inadequate to make definitive conclusions about relative effectiveness of inhaled corticosteroids and salmeterol in children with mild or moderate persistent asthma. Two randomized and double-blinded trials enrolled 116 (99 evaluable) children treated with inhaled corticosteroids, 112 (83 evaluable) children treated with salmeterol, and 80 (55 evaluable) children treated with placebo. One of these is a three-arm trial in which most comparisons were indirect and reported as inhaled corticosteroids vs. placebo and salmeterol vs. placebo. Of the statistically significant results reported, most were significant in only one of the two trials; however, all results clearly favored inhaled corticosteroids over salmeterol as monotherapy. In one of the trials, measurements of FEV_1 deteriorated over time in those children receiving monotherapy with salmeterol (Verberne et al. 1997).

Theophylline

One trial compared the effectiveness of 1 year of treatment with theophylline or low-dose inhaled corticosteroids in 747 patients, 185 of whom were children (Reed 1998). Although conclusions are limited because of the large numbers of withdrawals and the absence of additional trials, the data from this study support the superior effectiveness for low-dose inhaled corticosteroids compared to theophylline. The inhaled corticosteroids were significantly more effective in reducing symptoms, supplemental bronchodilators and systemic corticosteroid doses, bronchial hyperresponsiveness, and eosinophilia. No outcomes were significantly superior with theophylline, which caused more headaches, nervousness, insomnia, and gastrointestinal distress; and more patients discontinued treatment because of side effects that occurred while they were taking theophylline.

Nedocromil

The CAMP trial found no differences between nedocromil and placebo in lung function or symptom outcomes, although courses of oral corticosteroids and urgent care visits were reduced (CAMP 2000). The primary analysis in this study compares two medications—nedocromil and inhaled corticosteroids—to placebo, rather than to each other. However, the magnitude of the effect of inhaled corticosteroids on all clinical outcomes, along with the marginal effect of nedocromil on just two, supports the conclusion that inhaled corticosteroids are more effective than nedocromil in reducing the frequency and severity of symptoms, supplemental $beta_2$-agonist use, and the frequency of hospitalizations due to asthma.

Additional Literature/Information

Additional data were reviewed to include information that was published since the SRE was performed and to consider leukotriene modifiers.

Inhaled Corticosteroids

A recent study confirmed the effectiveness of inhaled corticosteroids in improving symptoms, airway hyperresponsiveness, and lung function in children 2 to 5 years of age (Nielsen and Bisgaard 2000).

Cromolyn and Nedocromil

A consideration of the precise relationship of cromolyn and nedocromil among other long-term-control medications in the treatment of persistent asthma continues to be difficult based on the few available comparison studies. These two medications have distinct properties but similar mechanisms of action. They have been shown to provide symptom control greater than placebo in some clinical trials (Konig 1997; Petty et al. 1989) and to confer protection against exacerbations of asthma leading to hospitalization, particularly in children (Donahue et al. 1997) and emergency department visits (Adams et al. 2001). These results, along with the excellent safety profile, justify consideration of these medications as treatment options. However, when data regarding the efficacy of cromolyn recently were systematically reviewed (Tasche et al. 2000), the authors concluded that insufficient evidence existed to conclude that cromolyn had a beneficial effect on maintenance treatment of childhood asthma. Compared to placebo, nedocromil reduces urgent care visits as well as the need for prednisone, which are meaningful clinical outcomes. However, nedocromil is no different than placebo on all other outcome measures (CAMP 2000). Overall, nedocromil is significantly less effective in improving outcome measures than inhaled corticosteroids (CAMP 2000). Nedocromil has not been adequately studied in children younger than 5 years of age.

As a result of these disparate findings on cromolyn and nedocromil (i.e., some, but limited effectiveness and strong safety profile), the Expert Panel's opinion is that cromolyn for children of all ages and nedocromil for children older than 5 years of age could be considered in the treatment of persistent asthma, but they are not preferred therapies (SRE-Evidence A; Evidence B, C).

Leukotriene Modifiers

Leukotriene modifiers comprise two pharmacologic classes of compounds: 5-lipoxygenase pathway inhibitors (e.g., zileuton), and LTRAs (e.g., zafirlukast and montelukast). Only zafirlukast (for children as young as 7 years of age) (Pearlman et al. 2000; Weinberger 2000) and montelukast (for children as young as 2 years of age) (Knorr et al. 1998; Knorr et al. 2001) are approved for use in children. Zileuton has been demonstrated to control asthma more effectively than placebo (Israel et al. 1996) and comparably to theophylline (Schwartz et al. 1998) in adult patients with persistent symptoms; studies in children have not been reported yet.

The LTRAs have been demonstrated to provide statistically significant but modest improvement in lung function when used as monotherapy in both adults and children as young as 6 years of age and in asthma control outcomes other than lung function in patients as young as 2 years of age (Pearlman et al. 2000; Knorr et al. 1998; Knorr et al. 2001; Israel et al. 1996; Schwartz et al. 1998; Altman et al. 1998; Busse et al. 2001; Kemp et al. 1998; Nathan et al. 1998; Tashkin et al. 1999; Bleecker et al. 2000; DuBuske et al. 1997). In general, these studies included patients with either mild or moderate persistent asthma, although the classification of severity was not always clear in the studies, nor consistently applied. When comparing overall efficacy of LTRAs to inhaled corticosteroids in adult patients with persistent asthma, most outcome measures significantly and clearly favored inhaled corticosteroids (Busse et al. 2001). Therefore, based on the available data comparing LTRAs to inhaled corticosteroids, the Expert Panel concludes that inhaled corticosteroids should be the preferred treatment option for mild persistent asthma in adults and, by extrapolation until published comparison data become available, for children (Evidence B, C). (See Medications: Combination Therapy for recommendations on the use of LTRAs in moderate asthma.) Due to the lack of randomized controlled trials (RCTs) in children less than 12 years of age, zileuton cannot be recommended for use in children.

Long-Acting Inhaled Beta$_2$-Agonists

In a recent study, 164 patients ages 12 through 65 years whose asthma was well controlled on 400 mcg twice daily of inhaled corticosteroids were randomly assigned to continue inhaled corticosteroids or switch to long-acting inhaled beta$_2$-agonists, 42 mcg twice daily. During the 16-week study, clinical outcomes did not differ significantly. However, those

on long-acting inhaled beta$_2$-agonists experienced significantly more treatment failures (24 percent vs. 6 percent) and asthma exacerbations (20 percent vs. 7 percent) than those remaining on inhaled corticosteroids (Lazarus et al. 2001). These results, favoring use of inhaled corticosteroids over long-acting beta$_2$-agonists as monotherapy, support the findings of the studies in children that were noted in the SRE.

Recommendations for EPR-2

The Expert Panel recommends revising EPR-2, based on review of the SRE and additional data and clinical experience. The following key changes are described:

- Based on the SRE, inhaled corticosteroids are the preferred treatment for initiating therapy in children of all ages with persistent asthma (SRE-Evidence A, B). Thus, the Expert Panel no longer recommends consideration of an initial therapeutic trial with cromolyn or nedocromil. Current scientific evidence demonstrates the superiority of inhaled corticosteroids.

- LTRAs are available for children as young as 2 years of age, and studies have demonstrated improved outcomes (Evidence B). LTRAs are an alternative—although not preferred—treatment (Evidence B) and are considered if patient circumstances regarding administration of inhaled corticosteroids warrants selection of oral treatment (Evidence D).

- Based on epidemiologic study of wheezing in early childhood, it is the opinion of the Expert Panel that the initiation of long-term-control therapy should be considered strongly for infants and young children who in the past year have had more than three episodes of wheezing that lasted more than 1 day and affected sleep, and who in addition have identifiable risk factors for the development of asthma (Evidence D). This is in addition to previously recommended indications for initiating long-term-control therapy (i.e., children requiring symptomatic treatment more than 2 times a week or experiencing severe exacerbations less than 6 weeks apart).

Specifically, the Expert Panel recommends that the text of EPR-2 be revised to read as follows in the EPR-2 sections: The Medications and the Stepwise Approach for Managing Asthma; the blue text indicates new text.

Recommended changes to The Medications (pages 59 through 67 in EPR-2)

Key Points: The Medications (page 59 in EPR-2):

- Cromolyn and nedocromil: Used as alternative, but not preferred, medications for the treatment of mild persistent asthma (Evidence A, B). Can also be used as preventive treatment prior to exercise or unavoidable exposure to known allergens.

- Long-acting inhaled beta$_2$-agonists: Long-acting bronchodilator used concomitantly with inhaled corticosteroids is the preferred combination therapy for long-term control and prevention of symptoms in moderate and severe persistent asthma (Evidence A, B). Also prevents exercise-induced bronchospasm (EIB).

- Leukotriene modifiers: The leukotriene receptor antagonists (LTRAs) montelukast (for patients ≥ 2 years of age) and zafirlukast (for patients ≥ 7 years of age), or the 5-lipoxygenase inhibitor zileuton (for patients ≥ 12 years of age), are alternative, but not preferred, treatments for the treatment of mild persistent asthma (Evidence A). Leukotriene modifiers may be used with inhaled corticosteroids as combination therapy in the treatment of moderate persistent asthma (Evidence B).

Corticosteroids (page 60 in EPR-2)

Insert after the third sentence.

The evidence of the efficacy of inhaled corticosteroids in children older than 5 years of age was obtained from six trials, five of which were placebo controlled and randomized (see EPR Update-2002 for complete references). Overall, these studies demonstrate that inhaled corticosteroids improve asthma control compared to as-needed beta$_2$-agonists without any other long-term-control medication (Evidence A). Inhaled corticosteroid-treated patients with mild or moderate persistent asthma demonstrate improvements in pre-bronchodilator FEV$_1$, reduced airway

hyperresponsiveness, symptom scores and symptom frequency, less supplemental beta$_2$-agonist use, fewer courses of oral corticosteroids, and lower hospitalization utilization. The evidence does not suggest, however, that inhaled [illegible] use is associated with improved [illegible] dilator FEV_1, which is [illegible] growth. No stud[illegible] y s[illegible] ly significant result that favored the [illegible]a$_2$-agonist control group. Studies com[illegible] inhale[illegible] osteroids to [illegible]molyn, nedo[illegible] neor[illegible] LTRAs are limited, but availa[illegible] evi[illegible] one of these long-term-cont[illegible] ations appear to be as effecti[illegible] inhaled cor[illegible] teroids in i[illegible] asthma out[illegible] nes (Evidence A, B).

Cromolyn Sodium and Nedocromil (page 60 in EPR-2)

Replace the third paragraph of text with the following.

Cromolyn sodium and [illegible]omil have b[illegible] n to provide symptom cont[illegible] greater than pl[illegible] bo in some clinical trials (Konig 199[illegible] ty et al. 19[illegible] and to confer protection against [illegible] acerbations of asthma leading to hospitalization, [illegible] cularly in children (Donahue et al. 1997) and e[illegible] rgency department visits (Adams et al. 2001) [illegible] e results, along with the excellent safety profile, jus[illegible] y consideration of these medications as treatment op[illegible]. However, when data regarding the efficacy of c[illegible] molyn recently were systematically reviewed (Tas[illegible] et al. 2000), the authors concluded that insufficient evidence existed to conclude that cromolyn had a beneficial effect on maintenance treatment of childhood asthma. Compared to placebo, nedocromil reduces urgent care visits as well as the need for prednisone, which are meaningful clinical outcomes. However, nedocromil is no different than placebo on all other outcome measures (CAMP 2000). Overall, nedocromil is significantly less effective in improving outcomes measures than inhaled corticosteroids (CAMP 2000). Nedocromil has not been adequately studied in children younger than 5 years of age. As a result of these disparate findings on cromolyn and nedocromil (i.e., some, but limited effectiveness and strong safety profile), the Expert Panel's opinion is that cromolyn for children of all ages and nedocromil for children older than 5 years of age could be considered in the treatment of persistent asthma, but they are not preferred therapies (Evidence A, B, C).

Leukotriene Modifiers (page 65 in EPR-2)

Replace the second paragraph of text with the following.

Three leukotriene modifiers—montelukast, zafirlukast and zileuton—are available as oral tablets for the treatment of asthma. Leukotriene modifiers comprise two pharmacologic classes of compounds: 5-lipoxygenase pathway inhibitors (e.g., zileuton), and LTRAs (e.g., montelukast and zafirlukast). Only zafirlukast (for children as young as 7 years of age) and montelukast (for children as young as 2 years of age) [illegible] approved for use in children. Zileuton has [illegible] onstrated to control asthma more effec[illegible] an placebo (Israel et al. 1996) and [illegible] parably to theophylline (Schwartz et al. 1998) in [illegible] atients with persistent symptoms; studies i[illegible] have [illegible] been reported yet.

[illegible] LTR[illegible] been demonstrated to provide stati[illegible] ificant but modest improvement in l[illegible] on w[illegible] sed as monotherapy in both [illegible]nd ch[illegible] young as 6 years of age and in [illegible]ma cor[illegible] com[illegible] ther than lung function in patients [illegible] f age (Pearlman et al. 2000; [illegible], Knorr et al. 2001; Israel et al. 199[illegible] z et al[illegible] man et al. 1998; Busse et al. 2001; K[illegible] Nathan et al. [illegible]998; Tashkin et [illegible] eec[illegible] al. 2000; DuBuske et al. [illegible] In g[illegible] e studies in[illegible] patients [illegible] or moderate pe[illegible] asthma, a[illegible] e classification of severi[illegible] ot always clear in the studies, nor consistently [illegible]ed. When comparing overall efficacy of LTRA[illegible] inhaled corticosteroids in adult patients with persistent asthma, most outcome measures significantly and clearly favored inhaled corticosteroids (Busse et al. 2001).

Insert as the final paragraph.

Therefore, based on the available data comparing LTRAs to inhaled corticosteroids, the Expert Panel concludes that inhaled corticosteroids should be the preferred treatment option for mild persistent asthma in adults, and by extrapolation until published com-

parison data become available, for children (Evidence B, C). Five published studies evaluated the addition of leukotriene modifiers to fixed doses of inhaled corticosteroids; none compared the combination to increasing the dose of inhaled c[illegible]s. Limitations of these stud[illegible]e conclusions, but t[illegible]rend[illegible]g improvement in [illegible]n a[illegible]me, symptoms fr[illegible] the combinati[illegible]ene modifiers and [illegible]ed corticosteroids [illegible]d with [illegible]d dose o[illegible]ed corticost[illegible]ne.

Figure 3–1. Long-Term-Control Medications (page 63 in EPR-2)

Long-Acting Inhaled Beta$_2$-Agonists. Add in "Therapeutic Issues" column: Treatmen[illegible]oice in combination with inhaled [illegible]icosteroids [illegible] ment of moderate persistent [illegible]ma in adul[illegible] children over 5 years of age.

Leukotriene Modifiers. Add: Mon[illegible]ukast tablets: long-term control and prevention of sym[illegible]s in mild persistent asthma for patients ≥2 y[illegible]s of age. May also be used with inhaled corticosteroi[illegible]s combination therapy in moderate persistent asthm[illegible] Zafirlukast: Change age zafirlukast to ≥7 years [illegible]. And add: May also be used with inhaled corticosteroids as combination therapy in moderate persistent asthma. Zileuton: add: May also be used with inhaled corticosteroids as combination therapy in moderate persistent asthma.

Figure 3–2. Quick-Relief Medications (page 64 in EPR-2)

Short-Acting Inhaled Beta$_2$-Agonists. Add: Levalbuterol

Recommended changes to The Stepwise Approach to Managing Asthma; mild persistent asthma (step 2 care) (pages 85 through 97 in EPR-2).

Revisions of EPR-2 on moderate persistent asthma (step 3 care) are presented in the section "Medications: Combination Therapy."

Figure 3–4b. Stepwise Approach for Managing Asthma in Adults and Children Older than 5 Years of Age: Treatment (page 85 in EPR-2)

Step 2
Mild Persistent
One daily long-term-control medication
Preferred treatment:
Inhaled corticosteroids (low dose)
Alternative treatment (listed alphabetically):
Cromolyn
OR
Leukotriene modifier (only LTRAs are recommended for use in children)
[illegible]R
[illegible]docrom[illegible]
[illegible]R
S[illegible]ease theophylline to serum [illegible]ions of 5–15 μg/mL.

Step 3 and Step 4
Please refer to the Medications: Combination Therapy on page 56 of this report.

Key Recommendations box for managing asthma in school-age children and adolescents (page 97 in EPR-2)

Pulmonary function testing should use appropriate reference populations. Adolescents compare better to childhood than to adult predicted norms.

- W[illegible] initiating daily [illegible]term-[illegible]erapy for mild [illegible]derate pe[illegible]nt th[illegible]e choice of medic[illegible]ncludes co[illegible]n of treatment effectiveness[illegible]dividual patient's history of previous respe[illegible]se[illegible] therapies, the ability of the patient and fa[illegible]y to correctly use the medication, and anticipated patient and family adherence with the treatment regime (Evidence D).

- Adolescents (and younger children when appropriate) should be directly involved in establishing goals for therapy and developing their asthma management plans.

- Active participation in physical activities, exercise, and sports should be promoted.

- A written asthma management plan should be prepared for the student's school and should include plans to ensure reliable, prompt access to medications. Either encour[illegible] parents to take a copy to the child's s[illegible] in parental permission and [illegible]ool nurse or desig[illegible]D).

Figure 3–6. Stepwise Approach for Managing Infants and Young Children (5 Years of Age and Younger) With Acute or Chronic Asthma Symptoms (page 96 in EPR-2)

Step 2
Mild Persistent
One daily [illegible]erm-control m[illegible]
Preferred tr[illegible]nt:
Low-dose in[illegible] corticost[illegible]h nebu-
lizer OR MDI [illegible]-holding c[illegible]with
without a face m[illegible]sk OR DPI)
Alternative treatment ([illegible] in alphabeti[illegible]
Cromolyn (nebulizer is p[illegible]erred; or MD[illegible]ith
holding chamber)
OR
Leukotriene receptor antagonis[illegible]

Step 3
Moderate Persistent
Preferred treatments:
Low-dose inhaled corticosteroids and lo[illegible]
acting inhaled $beta_2$-agonists
OR
Medium-dose inhaled corticosteroids
Alternative treatment:
Low-dose inhaled corticosteroids and either LTRA or theophylline.

If needed (particularly in patients with recurring severe exacerbations):
Preferred treatment:
Medium-dose inhaled corticosteroids and long-acting $beta_2$-agonists.
Alternative treatment:
Medium-dose inhaled corticosteroids and either LTRA or theophylline.

Special considerations for managing asthma in different groups: infants and young children (5 years of age and younger), key recommendations (pages 94 through 97 in EPR-2)

- Diagnosing asthma in infants is often difficult, yet underdiagnosis and undertreatment are key problems in this age group. Thus, a diagnostic trial of inhaled bronchodilators and anti-inflammatory medications may be helpful.

- Treatment for infants and young children with asthma has not been adequately studied. Recommendations for treatment are based on extrapolations from studies in older children and ad[illegible]ts.

[illegible]nitiation of long-term-control therapy [illegible]ould be strongly considered in the following [illegible]stances, in the opinion of the Expert Panel [illegible]ice D):

- Inf[illegible]young children who had more [illegible]e[illegible]isodes of wheezing in the past [illegible]hat l[illegible] more than 1 day and affected [illegible]eep A[illegible] have a high risk of developing pers[illegible]thma[illegible]indicated by either (a) a ph[illegible]di[illegible]topic dermatitis or a [illegible] asthma OR (b) two of the fo[illegible]conditio[illegible]n-diagnosed allergic rhiniti[illegible]ercent periph-eral blood e[illegible]or [illegible]ing apart from colds (Mar[illegible]et al. [illegible]tinez 1995; [illegible]stro-Rod[illegible]00).

- Infants and young children consistently requiring symptomatic treatment more than 2 times per week should be given daily long-term-control therapy.

- Infants and young children who have severe exacerbations (requiring inhaled $beta_2$-agonist more frequently than every 4 hours over 24 hours) that occur less than 6 weeks apart.

- When initiating daily long-term-control therapy, inhaled corticosteroids are the preferred treatment (SRE-Evidence B). Alternative treatment options (listed here in alphabetical order because there are insufficient data to enable ranking) include cromolyn and LTRA (moderate evidence B). The initial choice of long-term-control medication includes consideration of treatment effectiveness, the individual patient's previous response to therapies, the severity of the patient and the ability to correctly use medications, and anticipated patient and family adherence to treatment regimen (Evidence D).

- Response to therapy should be carefully monitored. Once control of asthma symptoms is established and sustained, a careful step down in therapy should be attempted. If clear benefit is not observed within 4 to 6 weeks, alternative therapies or diagnoses should be considered (Evidence D).

Diagnosis

Several studies show that as many as 50 to 80 percent of children with asthma develop symptoms before their fifth birthdays. Diagnosis can be difficult in this age group and has important implications. On the one hand, asthma in early childhood is frequently underdiagnosed (receiving such labels as chronic bronchitis, wheezy bronchitis, recurrent pneumonia, gastroesophageal reflux, and recurrent upper respiratory tract infections), and thus many infants and young children do not receive adequate therapy. On the other hand, not all wheezes and coughs are caused by asthma, and caution is needed to avoid giving infants and young children inappropriately prolonged asthma therapy. Episodic or chronic wheezing, coughing, and breathlessness also may be seen in other less common conditions, including cystic fibrosis, vascular ring, tracheomalacia, primary immunodeficiency, congenital heart disease, parasitic disease, and foreign body aspiration.

Among children 5 years of age and younger, the most common cause of asthma-like symptoms is viral respiratory infection. At present, the relative contributions of airway inflammation, bronchial smooth-muscle abnormalities, or other structural factors in producing wheeze with acute viral upper respiratory infections are unknown. There appear to be two general patterns of illness in infants and children who wheeze with acute viral upper respiratory infections: a remission of symptoms in the preschool years and persistence of asthma throughout childhood. No clear markers are available to predict the prognosis of an individual child; however, in infants and young children under 5 years of age with frequent wheezing (for example, more than three episodes in the past year that lasted more than 1 day and affected sleep), risk factors significantly associated with persistent asthma at 6 years of age include having either (a) parental asthma history or a physician diagnosis of atopic dermatitis or (b) two of the following conditions: physician-diagnosed allergic rhinitis, peripheral blood eosinophilia, or wheezing apart from colds (Evidence C) (Castro-Rodriguez et al., 2000; Martinez et al., 1995). Although currently not established, it is conceivable that early recognition and treatment of these high-risk children could alter the natural history and prevention of childhood asthma.

Diagnosis is complicated by the difficulty in obtaining objective measurements of lung function in this age group. Essential elements in the evaluation include the history, symptoms, physical examination, and assessment of quality of life. A therapeutic trial with medications listed in figure 3–5d also will aid in the diagnosis.

Treatment

Figure 3–6 illustrates the Expert Panel's recommendations for a stepwise approach to managing acute and chronic asthma symptoms, regardless of the prognosis for the wheezing infant or young child.

It is the opinion of the Expert Panel that, in general, daily long-term-control therapy should be initiated in infants and young children consistently requiring symptomatic treatment more than 2 times per week and in infants and young children who experience severe exacerbations (requiring inhaled $beta_2$-agonist more frequently than every 4 hours over 24 hours) that occur less than 6 weeks apart. It is the opinion of the Expert Panel that the initiation of long-term-control therapy should also be strongly considered in infants and young children who had more than three episodes of wheezing in the past year that lasted more than 1 day and

affected sleep AND who have risk factors for developing persistent asthma: either (a) parental history of asthma or a physician diagnosis of atopic dermatitis or (b) two of the following conditions: physician [illegible] allergic rhinitis, greater than 4 [illegible] blood eosinophils, wheezing [illegible] from colds (Evidence [illegible]).

The following have been approved by the Food and Drug Administration (FDA) [illegible] for children: the inhaled corticosteroids budesonide solution (approved for children 12 months through 8 years of age) and fluticasone DPI (approved for children 4 years and older); the long-acting beta$_2$-agonist salmeterol (approved for children 4 years of age and older); based on safety data rather than efficacy data, the LTRA montelukast 4-mg chewable tablet (approved for children 2 to 5 years of age).

At present, there are few studies of medications in children younger than 3 years of age. A therapeutic trial of anti-inflammatory medications should be monitored carefully. Treatment should be stopped if a clear beneficial effect is not obvious within 4 to 6 weeks. Inhaled corticosteroids have been shown to be effective in long-term clinical studies with infants; in contrast, cromolyn has inconsistently demonstrated symptom control in children younger than 5 years of age (Tasche et al. 2000). A LTRA (montelukast 4-mg chewable tablet has shown some effectiveness in children 2 to 5 years of age (Knorr et al. 2001). Sustained-release theophylline is not recommended as an alternative long-term-control medication for young children with mild persistent asthma because it may have particular risks of adverse side effects in infants who frequently have febrile illnesses, which increase theophylline concentrations. Theophylline may be considered as adjunctive therapy in young children with moderate or severe persistent asthma if there are cost considerations, but only if serum concentration levels will be carefully monitored.

In deciding when to initiate daily long-term-control therapy, the clinician must weigh the possible long-term effects of inadequately controlled asthma vs. the possible adverse effects of medications given over prolonged periods. There is evidence that anti-inflammatory treatment can reduce morbidity from wheezing in early childhood (Connett et al. 1993). Long-term studies in children 5 to 12 years of age at the time of enrollment conclude that inhaled corticosteroids improve health outcomes for children with mild or moderate persistent asthma and that the potential albeit small risk of delayed growth from the use of inhaled corticosteroids is well balanced by their effectiveness (CAMP 2000). Further, available long-term data indicate that most children treated with recommended doses of inhaled corticosteroids achieve their predicted adult heights (Agertoft and Pedersen 2000). It is noted that the long-term prospective studies on growth involved budesonide, and that the retrospective analyses included studies on beclomethasone, but the results have been generalized to include all inhaled corticosteroid preparations. Although different preparations and delivery devices may have a systemic effect at different doses, all short-term studies on numerous preparations suggest that the effect of inhaled corticosteroids on growth is a drug class effect. In children demonstrating adverse effects related to inhaled corticosteroid therapy, other options (cromolyn, LTRA, nedocromil or theophylline) for initiating maintaining long-term-control therapy are available. The [illegible] based on high-quality evidence, the Expert Panel recommends long-term-control therapy [illegible] with mild or moderate persistent asthma because it provides control of [illegible] asthma symptoms (SRE-Evidence A). [illegible] evidence to date is insufficient to [illegible] regarding whether early [illegible] delayed [illegible] with daily long-term-control medication will alter the underlying course of disease. Although a preliminary study suggests that appropriate control of childhood asthma may prevent more serious asthma of irreversible obstruction in later years (Agertoft and Pedersen 1994), these observations were not verified in a recent long-term randomized controlled trial in children ages 5 to 12 years (CAMP 2000). The best available evidence does not support the assumption that children 5 to 12 years of age with mild or moderate persistent asthma have a progressive decline in lung function that can be prevented by early initiation of long-term-control medications. Observational prospective data from other large groups of children suggest that the timing of the CAMP intervention was too late, as

most loss of lung function in early childhood asthma appears to occur during the first 3 to 5 years of life (Martinez et al. 1995). However, it has not yet been determined whether early recognition of children at high risk of developing persistent asthma coupled with early intervention will either prevent the onset of lung dysfunction or prevent the development of persistent disease. Current critical prospective studies to address these issues are in progress.

Recommendations for treating infants and young children at different steps of care include:

- The patient's response to therapy should be monitored carefully. When benefits are sustained for 2 to 4 months, a step down in therapy should be attempted. If there are no clear benefits within 4 to 6 weeks, treatment should be stopped and alternative therapies or diagnoses should be considered (Evidence D).

- For step 2 care (mild persistent asthma), daily long-term-control therapy with an inhaled corticosteroid is the preferred option. Cromolyn and LTRA are alternative therapies (SRE-Evidence A, B; Evidence B). A trial of LTRA in children 2 years of age or older can be considered in situations in which inhaled medication delivery is suboptimal due to poor technique or adherence (Evidence D).

- When inhaled corticosteroids are introduced in step 2 care, doses should be in the low range. Inhaled corticosteroids are now available in both MDI and nebulizer preparations. (See figures 3–5b and 3–5c in EPR-2 for discussion of equivalency among preparations.)

- For step 3 care (moderate persistent asthma), there are no data available that compare treatments in step 3 care for infants and young children whose asthma is not well controlled on low doses of inhaled corticosteroids. Recommendations are based on expert opinion and extrapolation from studies in older patients. (See Medications: Combination Therapy.) There are two main choices for step 3 care therapy: adding long-acting inhaled $beta_2$-agonists to low-dose inhaled corticosteroids (SRE-Evidence B; extrapolation from studies in older children) OR increasing the dose of inhaled corticosteroids within the medium-dose range (Evidence D). Alternative but not preferred options are adding either a LTRA or theophylline (if serum concentrations are monitored) to low-to-medium doses of inhaled corticosteroids (Evidence D).

Comparative studies in older children and adults consistently favor combination therapy over increasing doses of inhaled corticosteroids. Because studies indicate that the potential for side effects of inhaled corticosteroids, though small, appears to be dose related and has been demonstrated in this age group at the medium-dose range of inhaled corticosteroids (Bisgaard 2002), the approach of adding long-acting inhaled $beta_2$-agonists to a lower dose of inhaled corticosteroids is one preferred option (Evidence D, extrapolation from adult studies). On the other hand, there are no data on long-acting $beta_2$-agonists in children under 4 years of age, and studies in infants and young children have shown medium dose inhaled corticosteroids to be effective in managing moderate and severe asthma (Connett 1995, de Blic 1996, Bisgaard 1999, Nielsen 2000). The studies available in this age group that directly considered different doses of inhaled corticosteroids have shown that increasing the dose is most effective in reducing asthma exacerbations (Bisgaard 1999) and less consistently effective in other outcomes (Bisgaard 1999, Connett 1995, de Blic 1996, Nielsen 2000). These results also have been confirmed in studies of adults. Therefore, it is the opinion of the Expert Panel that adding medium doses of inhaled corticosteroids as initial therapy for moderate asthma is another preferred treatment option.

For all treatments, it is essential to monitor the child's response to therapy. If there is no clear response within 4 to 6 weeks, the therapy should be discontinued and alternative therapies or alternative diagnoses considered. If there is a clear and positive response after 2 to 4 months, a step down in therapy should be undertaken to the lowest possible doses of medication required to maintain asthma control (Baker 1999; Kemp, Skoner, Szefler et al. 1999).

- Exacerbations caused by viral respiratory infections may be intermittent yet severe. Consider systemic corticosteroids if the exacerbation is moderate to severe or at the onset of a viral respiratory infection if the patient has a history of severe exacerbations.

- Consultation with an asthma specialist should be *considered* for infants and young children requiring step 2 care; consultation is *recommended* for those requiring step 3 or step 4 care.

- Several delivery devices are available for infants and young children. The dose received may vary considerably among devices and age groups. (See figure 3–3 for a summary of therapeutic issues regarding aerosol delivery devices.) The child's caregivers must be instructed in the proper use of appropriately sized face masks, spacers/holding chambers with face masks, and spacers/holding chambers for medication delivery to be effective and efficient. For children 2 years of age and younger, nebulizer therapy with mask may be preferred for administering aerosol medications. Children between 3 and 5 years of age may begin therapy with MDI and spacer/holding chamber alone, but if the desired therapeutic effects are not achieved, they may require a nebulizer or an MDI plus spacer/holding chamber and face mask.

Recommendations for Future Research

- How do LTRAs and inhaled corticosteroids compare in safety and efficacy in both the short term and long term in the treatment of mild persistent asthma in children younger than 5 years of age?

- Do anticipated differences in adherence to medication regimens (for example, inhalation therapy vs. oral tablet dose therapy) translate into significant clinical differences in overall asthma control?

- What is the best form of adjunctive therapy in children with moderate persistent asthma who are not adequately controlled on inhaled corticosteroid therapy alone? Long acting $beta_2$-agonists? LTRAs? Theophylline?

  Can response to various long-term-control medications be predicted prior to initiating treatment? Phenotype and genotype characterizations and definitions are needed to address this question.

- What is the most effective way of treating children who have only viral-induced asthma symptoms?

- Is drug delivery using an MDI with spacer equal in efficacy to nebulizer treatments in childhood asthma?

- Can early recognition and treatment of an infant or young child at high risk of developing asthma prevent development of persistent asthma?

Key Evidence Tables

Table 1-1. Inhaled Corticosteroids vs. No Inhaled Corticosteroids

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD	Estimated Disease Severity	
Children older than 5 years						
Childhood Asthma Management Research Group 2000a Randomized, parallel-arm, double-blinded, placebo-controlled trial	Placebo	418	411	9 +/- 2.2	Mild or Moderate	
	BUD	311	306	9 +/- 2.1	Mild or Moderate	
Jonasson, Carlsen, Blomqvist 1998 Randomized, parallel-arm, double-blinded, placebo-controlled trial	Placebo	40	40	9.6	Mild	
	BUD 1 BUD 2 BUD 3	40 42 41	40 42 41	10.2 10.0 9.8	Mild Mild Mild	
Simons 1997 Randomized, parallel-arm, double-blinded, placebo-controlled trial	Placebo	55	52	9.5 +/- 2.4	Mild or Moderate	
	BDP	81	67	9.6 +/- 2.6	Mild or Moderate	
Hoekstra, Grol, Hovenga et al. 1998 Randomized, parallel-arm, double-blinded, placebo-controlled trial	Placebo	19	15	11 +/- 1.8	Mild or Moderate	
	FP	15	25	10.6 +/- 1.8	Mild or Moderate	
Agertoft and Pedersen 1994 Parallel-arm-controlled trial	Placebo	62	NR	6.1	Mild or Severe	
	BUD	216	NR	6.2	Mild or Severe	
van Essen-Zandvliet, Hughes, Waalkens et al. 1992 Randomized, parallel-arm, double-blinded, placebo-controlled trial	Placebo	58	17	10.9 +/- 1.9	Mild or Severe	
	BUD	58	29	11 +/- 1.9	Mild or Severe	
Children younger than 5 years						
Storr, Lenney, Lenney 1986 Randomized, parallel-arm, double-blinded, placebo-controlled trial	Placebo	14	13	3.4 +/- 1.5	Unable to estimate	
	BDP	15	15	3.6 +/- 1.2	Unable to estimate	
Connett, Warde, Wooler et al. 1993 Randomizitrolled trial	Placebo	20	19	1.9 +/- 0.5	Unable to estimate	
	BUD	20	17	1.7 +/- 0.6	Unable to estimate	

Key:
BDP = beclomethasone dipropionate
FP = fluticasone propionate
SD = standard deviation
BUD = budesonide
NR = not reported
Sx = symptom
FEV_1 = forced expiratory flow volume in 1 second
PC20 = provocative concentration of bronchoconstrictor that induces a 20% drop in FEV_1
PEF = peak expiratory flow
X = outcome reported

	Study Duration (weeks)	Lung Fu...	...comes PC20	Sx/Meds	Utilization Outcomes	Comments
	224	X	X	X	X	X	
	224	X	X	X	X	X	
	12	X	X	X	X		Not stated how patients with moderate-severe asthma were excluded.
	12	X	X	X	X		
	12	X	X	X	X		
	12	X	X	X	X		
	52	X	X	X	X	X	
	52	X	X	X	X	X	
	12	X	X	X			
	12	X	X	X			
	270.4 (mean)	X				X	Control patients were those patients who declined recommendation to take inhaled corticosteroids. Inhaled corticosteroid-free period after diagnosis is referred to as the run-in period, equal to at least 1 year.
	192.4 (mean)	X				X	
	95.3 (median)	X	X	X		X	
	95.3 (median)	X	X	X		X	Pharmaceutical company supplied study medication.
	26				X		Study took place over an 18-month period in an attempt to eliminate seasonal bias.
	26				X		
	26				X	X	Patients treated for up to 6 months, included in analysis if treated at least 5 weeks.
	26				X	X	Study medication adjusted to 200–400 mcg 2x/day budesonide or 1–2 puffs 2x/day placebo depending on clinical need.

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. *Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44.* AHRQ Publication No. 01-E044. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.

Table 1-2a. Inhaled Corticosteroids vs. Long-Acting Inhaled $Beta_2$-Agonists

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD	Estimated Disease Severity	
Verberne, Frost, Roorda et al. 1997	Salmeterol	35	25	10.6 +/- 2.9	Mild or Moderate	
Randomized, parallel-arm, double-blinded, controlled trial	BDP	35	32	10.5 +/- 2.3	Mild or Moderate	
Simons 1997	BDP	81	67	9.6 +/- 2.6	Mild or Moderate	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	Salmeterol	80	58	8.8 +/- 2.1	Mild or Moderate	

Table 1-2b. Inhaled Corticosteroids vs. Theophylline

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD	Estimated Disease Severity	
Tinkelman, Reed, Nelson, et al. 1993	Theophylline	93	69	11.9 +/- 2.8	Mild or Severe	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BDP	102	76	11.9 +/- 2.7	Mild or Severe	

Table 1-2c. Inhaled Corticosteroids vs. Nedocromil

Citation/Study Type	Study Arm	Number Enrolled	Number Evaluable	Mean Age +/- SD	Estimated Disease Severity	
Childhood Asthma Management Program Research Group 2000a	Placebo	418	411	9 +/- 2.2	Mild or Moderate	
Randomized, parallel-arm, double-blinded, placebo-controlled trial	BUD	311	306	9 +/- 2.1	Mild or Moderate	

	Study Duration (weeks)	Lung Function Outcomes			Sx/Meds	Utilization Outcomes	Comments
				PC20			
	48	X	X	X			
	48	X	X	X			
	52	X	X	X		X	
	52	X	X	X		X	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001

	Study Duration (weeks)	Lung Function Outcomes			Sx/Meds	Utilization Outcomes	Comments
		FEV_1	PEF	PC20			
	36	X	X	X	X	X	
	36	X	X	X	X	X	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001

	Study Duration (weeks)	Lung Function Outcomes			Sx/Meds	Utilization Outcomes	Comments
		FEV_1	PEF	PC20			
	224	X	X	X	X	X	
	224	X	X	X	X	X	

Source:
Blue Cross and Blue Shield Association Technology Evaluation Center. Management of Chronic Asthma: Evidence Report/Technology Assessment Number 44. AHRQ Publication No. 01-EO44. Rockville, MD: Agency for Healthcare Research and Quality. September 2001.